HEXAMETHYLPHOSPHORAMIDE

Data were last reviewed in IARC (1977) and the compound was classified in *IARC Monographs* Supplement 7 (1987).

1. Exposure Data

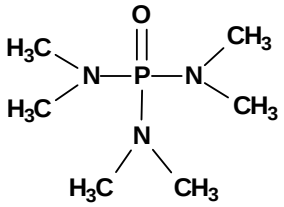
1.1 Chemical and physical data

1.1.1 *Nomenclature*

Chem. Abstr. Serv. Reg. No.: 680-31-9

Systematic name: Hexamethylphosphoric triamide

1.1.2 *Structural and molecular formulae and relative molecular mass*



$C_6H_{18}N_3OP$ Relative molecular mass: 179.2

1.1.3 *Physical properties* (for details, see IARC, 1977)

(*a*) *Melting-point*: 7°C

(*b*) *Boiling-point*: 233°C

(*c*) *Conversion factor*: $mg/m^3 = 7.33 \times ppm$

1.2 Production and use

Hexamethylphosphoramide has been produced commercially in relatively small quantities in several countries of Europe, in Japan and in the United States. It is used as a solvent for polymers, a selective solvent for gases and as a thermal and ultraviolet radiation degradation stabilizer in various polymers (IARC, 1977).

2. Studies of Cancer in Humans

No data were available to the Working Group.

3. Studies of Cancer in Experimental Animals

Hexamethylphosphoramide was tested for carcinogenicity in rats, the only species tested, by inhalation; in this study, which was reported as a preliminary note, it produced squamous-cell carcinomas of the nasal cavity. It has also been inadequately tested in rats by oral administration (IARC, 1977).

3.1 Inhalation exposure

Rat: Four groups of 120 male and 120 female Sprague-Dawley rats were exposed to 0 (control), 50, 400 and 4000 ppb [0, 0.37, 2.9 and 29 mg/m^3] hexamethylphosphoramide vapour for 6 h per day on five days per week for periods ranging from nine months to two years. In an additional study, four groups of 100 male and 100 female rats were similarly exposed to 0, 10, 50 and 100 ppb [0, 73, 370 and 730 µg/m^3] atmospheres. Nasal tumours were first found after approximately seven months of exposure at 400 and 4000 ppb, after nine months at 100 ppb and after 12 months at 50 ppb. No exposure-related tumours were found at 10 ppb. Tumour incidences at 24 months were: 50 ppb, 15% (12 months of exposure) and 25% (24 months of exposure); 100 ppb, 19% (six months of exposure) and 56% (13 months of exposure); 400 ppb, 82% (10 months of exposure); 4000 ppb, 83% (nine months of exposure). Most tumours developed in the squamous or respiratory epithelium and nasal glands, all of which showed squamous metaplasia or dysplasia in the anterior nasal cavity. Exposure concentrations correlated with tumour incidence and latency, but not with tumour type. The total of 473 nasal tumours included 72% epidermoid carcinomas, 15% adenoid squamous carcinomas and 8% papillomas. Most tumours (59%) developed in the anterior nasal cavity and then progressed to the posterior nasal cavity (41%) (Lee & Trochimowicz, 1982a).

4. Other Data Relevant to an Evaluation of Carcinogenicity and its Mechanisms

4.1 Absorption, distribution, metabolism and excretion

4.1.1 *Humans*

No data were available to the Working Group.

4.1.2 *Experimental systems*

When labelled hexamethylphosphoramide was given intraperitoneally to rats and mice, 70% of the label was excreted within 20 h in the urine. The parent compound undergoes a sequence of *N*-demethylations to yield pentamethylphosphoramide, *N*′,*N*′,*N*′′,*N*′′′-tetramethylphosphoramide and *N*′,*N*′′,*N*′′′-trimethylphosphoramide. In-vitro studies with rat liver slices indicated oxidative demethylation with the simultaneous formation of

formaldehyde. Hexamethylphosphoramide is also excreted in cows' milk after oral administration (IARC, 1977).

4.2 Toxic effects

4.2.1 *Humans*

No data were available to the Working Group.

4.2.2 *Experimental systems*

Repeated inhalation of hexamethylphosphoramide by rats resulted in severe degenerative changes in renal convoluted tubules. Rats given this compound in the diet showed severe bronchiectasis and bronchopneumonia with areas of squamous metaplasia (IARC, 1977).

Inhalation by rats of 351 ppm [*sic*] for 15 min did not cause any decrease in respiratory rate (Gardner *et al*., 1985). In the carcinogenicity experiment described above (Lee & Trochimowicz, 1982a), rhinitis, nasal epithelium degeneration, squamous metaplasia and dysplasia were observed in rats exposed to hexamethylphosphoramide by inhalation at concentrations of 10, 50, 100, 400 or 4000 ppb for 6–24 months. No pathological lesions were found in the 10-ppb group after 24 months. Incidence of tracheitis, degeneration of the tracheobronchial epithelium and murine pneumonia was dose-related in the 100-, 400- and 4000-ppb groups. The ciliated cells were the most susceptible to hexamethylphosphoramide. Keratinized squamous metaplasia developed at 4000 ppb (Lee & Trochimowicz, 1982b,c).

4.3 Reproductive and developmental effects

4.3.1 *Humans*

No data were available to the Working Group.

4.3.2 *Experimental systems*

When rats were given daily doses of 200 mg/kg bw hexamethylphosphoramide on days 7–20 of gestation, no abnormalities were found in the offspring. The fertility of rats was not impaired by 10 mg/kg bw per day administered by gavage for 169 days (IARC, 1977).

4.4 Genetic and related effects

4.4.1 *Humans*

No data were available to the Working Group.

4.4.2 *Experimental systems* (see Table 1 for references)

Hexamethylphosphoramide gave negative results in several conventional assays for bacterial mutagenicity which employed commonly used *Salmonella typhimurium* strains in the presence or absence of exogenous metabolic activation systems. In one study, it gave positive results in two strains of *Escherichia coli* WP2, in the presence of an

Table 1. Genetic and related effects of hexamethylphosphoramide

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
SAF, *Salmonella typhimurium*, forward mutation, 8-azaguanine	NT	–	1000	Skopek *et al.* (1981)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	NG	Baker & Bonin (1981)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	1000	Brooks & Dean (1981)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	NG	Garner *et al.* (1981)
SA0, *Salmonella typhimurium* TA100, reverse mutation (fluctuation test)	–	–	500	Hubbard *et al.* (1981)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	5000	MacDonald (1981)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	NG	Martire *et al.* (1981)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	NG	Nagao & Takahashi (1981)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	500	Richold & Jones (1981)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	1000	Rowland & Severn (1981)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	NG	Simmon & Shepherd (1981)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	NG	Venitt & Crofton-Sleigh (1981)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	5000	Zeiger & Haworth (1985)
SA0, *Salmonella typhimurium* TA100, reverse mutation (liquid suspension test)	–	+	2000	Sarrif *et al.* (1997)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	NG	Baker & Bonin (1981)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	1000	Brooks & Dean (1981)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	NG	Martire *et al.* (1981)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	NG	Garner *et al.* (1981)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	500	Richold & Jones (1981)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	1000	Rowland & Severn (1981)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	NG	Simmon & Shepherd (1981)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	5000	Zeiger & Haworth (1985)

Table 1 (contd)

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
SA5, *Salmonella typhimurium* TA1535, reverse mutation (liquid suspension test)	–	–	40000	Sarrif *et al.* (1997)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	NG	Baker & Bonin (1981)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	1000	Brooks & Dean (1981)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	NG	Martire *et al.* (1981)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	NG	Garner *et al.* (1981)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	2500	MacDonald (1981)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	NG	Nagao & Takahashi (1981)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	500	Richold & Jones (1981)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	1000	Rowland & Severn (1981)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	NG	Simmon & Shepherd (1981)
SA7, *Salmonella typhimurium* TA1537, reverse mutation (liquid suspension test)	–	+	10000	Sarrif *et al.* (1997)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	NG	Baker & Bonin (1981)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	1000	Brooks & Dean (1981)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	NG	Martire *et al.* (1981)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	500	Richold & Jones (1981)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	1000	Rowland & Severn (1981)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	NG	Simmon & Shepherd (1981)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	NG	Baker & Bonin (1981)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	1000	Brooks & Dean (1981)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	NG	Martire *et al.* (1981)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	NG	Garner *et al.* (1981)
SA9, *Salmonella typhimurium* TA98, reverse mutation (fluctuation test)	–	–	500	Hubbard *et al.* (1981)

Table 1 (contd)

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	5000	MacDonald (1981)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	NG	Nagao & Takahashi (1981)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	500	Richold & Jones (1981)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	1000	Rowland & Severn (1981)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	NG	Simmon & Shepherd (1981)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	NG	Venitt & Crofton-Sleigh (1981)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	5000	Zeiger & Haworth (1985)
SA9, *Salmonella typhimurium* TA98, reverse mutation (liquid suspension test)	–	+	10000	Sarrif *et al.* (1997)
SAS, *Salmonella typhimurium* TA92, reverse mutation	–	–	1000	Brooks & Dean (1981)
SAS, *Salmonella typhimurium* TA97, reverse mutation	–	–	5000	Zeiger & Haworth (1985)
SAS, *Salmonella typhimurium* TA97, reverse mutation (liquid suspension test)	–	+	5000	Sarrif *et al.* (1997)
ECK, *Escherichia coli* K-12/343/113, forward or reverse mutation	–	–	4000	Mohn *et al.* (1981)
ECW, *Escherichia coli* WP2 *uvr*A, reverse mutation	–	+	NG	Venitt & Crofton-Sleigh (1981)
EC2, *Escherichia coli* WP2, reverse mutation	–	+	NG	Venitt & Crofton-Sleigh (1981)
ECW, *Escherichia coli* WP2*uvrA*, reverse mutation (fluctuation test)	–	–	1000	Gatehouse (1981)
EC2, *Escherichia coli* WP2, reverse mutation	–	–	NG	Matsushima *et al.* (1981)
ECW, *Escherichia coli* WP2*uvr*A, reverse mutation	–	–	NG	Matsushima *et al.* (1981)
ECR, *Escherichia coli* WP2*uvr*ApKM101, reverse mutation	–	–	NG	Matsushima *et al.* (1981)
SCH, *Saccharomyces cerevisiae* JD1, homozygosis by mitotic gene conversion	–	+	50	Sharp & Parry (1981)

Table 1 (contd)

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
SCH, *Saccharomyces cerevisiae D7*, homozygosis by mitotic gene conversion	–	+	2000	Zimmermann & Scheel (1981)
SCH, *Saccharomyces cerevisiae* DEL, homozygosis by mitotic gene conversion	(+)	(+)	50000	Carls & Schiestl (1994)
SCR, *Saccharomyces cerevisiae* XV-185-14C, reverse mutation	–	(+)	100	Mehta & von Borstel (1981)
SZF, *Schizosaccharomyces pombe*, forward mutation, five loci	–	–	30	Loprieno (1981)
DMM, *Drosophila melanogaster*, *white/white*$^+$ eye mosaic test, somatic mutation and mitotic recombination	+		18 feed	Vogel & Nivard (1993)
DMM, *Drosophila melanogaster*, *white/white*$^+$ eye mosaic test, somatic mutation and mitotic recombination host (SMART)	+		18 feed	Aguirrezabalaga *et al.* (1994)
DMM, *Drosophila melanogaster*, *white-ivory* eye test, somatic mutation and mitotic recombination	+		9 feed	Ferreiro *et al.* (1995)
DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutations	+		250 ppm feed	Valencia & Houtchens (1981)
DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutations	+		100 feed	Vogel *et al.* (1981)
DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutations	+		100 feed	Wurgler & Graf (1981)
DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutations	+		25 feed	Vogel *et al.* (1985)
DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutations	+		100 ppm feed	Foureman *et al.* (1994)
DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutations	+		45 feed	Aguirrezabalaga *et al.* (1995)
DMH, *Drosophila melanogaster*, heritable translocation test	+		25 feed	Vogel *et al.* (1985)
DMH, *Drosophila melanogaster*, heritable translocation test	+		100 ppm feed	Foureman *et al.* (1994)
Drosophila melanogaster, survival of DNA repair-deficient mus homozygotes relative to their repair-proficient heterozygous siblings	+		896 feed	Henderson & Grigliatti (1992)
Micronucleus test, *Pleurodeles waltl in vivo*	(+)		30	Fernandez *et al.* (1989)
DIA, DNA–protein cross-links, rat nasal epithelial cells *in vitro*	+	NT	179	Kuykendall *et al.* (1995)

Table 1 (contd)

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
GCO, Gene mutation, Chinese hamster ovary CHO cells *in vitro*, five loci	–	–	31000	Carver *et al.* (1981)
DMN, *Drosophila melanogaster*, chromosome loss (ring-X)	+		11 feed	Vogel *et al.* (1985)
G9H, Gene mutation, Chinese hamster lung V79 cells, *hprt* locus *in vitro*	–	?	200	Knaap *et al.* (1981)
GML, Gene mutation, mouse lymphoma P388F cells *tk* locus *in vitro*	NT	+	8.28	Anderson & Cross (1985)
G5T, Gene mutation, mouse lymphoma L5178Y cells, *tk* locus *in vitro*	–	+	1500	Jotz & Mitchell (1981)
SIC, Sister chromatid exchange, Chinese hamster ovary CHO cells *in vitro*	–	–	1000	Evans & Mitchell (1981)
SIC, Sister chromatid exchange, Chinese hamster ovary CHO cells *in vitro*	–	–	339	Natarajan & van Kesteren-van Leeuwen (1981)
SIC, Sister chromatid exchange, Chinese hamster ovary CHO cells *in vitro*	–	+	10	Perry & Thomson (1981)
SIC, Sister chromatid exchange, Chinese hamster ovary CHO cells *in vitro*	–	+[c]	5.4	Darroudi & Natarajan (1993)
MIA, Micronucleus test, Chinese hamster ovary CHO cells *in vitro*	–	+[c]	2.7	Darroudi & Natarajan (1993)
CIC, Chromosomal aberrations, Chinese hamster ovary CHO cells *in vitro*	–	–	339	Natarajan & van Kesteren-van Leeuwen (1981)
CIR, Chromosomal aberrations, rat liver RL_1 cells *in vitro*	–	NT	100	Dean (1981)
SIH, Sister chromatid exchange, human hepatoma Hep G2 cells *in vitro*	+	NT	1.6	Natarajan & Darroudi (1991)
MIH, Micronucleus test, human hepatoma Hep G2 cells *in vitro*	+	NT	1.6	Natarajan & Darroudi (1991)
MIH, Micronucleus test, human hepatoma Hep G2 cells *in vitro*	+[d]	NT	0.5	Darroudi *et al.* (1996)
MIH, Micronucleus test, human lymphocytes *in vitro*	–	NT	1.8	Darroudi *et al.* (1996)
CHL, Chromosomal aberrations, human lymphocytes *in vitro*	–	NT	900	Chang & Klassen (1968)
SVA, Sister chromatid exchange, CBA/J mouse bone marrow *in vivo*	+		15.4 ip × 1	Paika *et al.* (1981)

Table 1 (contd)

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
SVA, Sister chromatid exchange, CBA/J mouse liver *in vivo*	–		1304 ip × 1	Paika *et al.* (1981)
MVM, Micronucleus test, $B6C3F_1$ mouse bone marrow *in vivo*	+		1232 ip × 2	Salamone *et al.* (1981)
MVM, Micronucleus test, ICR mouse bone marrow *in vivo*	+		205 ip × 2	Kirkhart (1981)
MVM, Micronucleus test, CDI mouse bone marrow *in vivo*	+		205 ip × 2	Tsuchimoto & Matter (1981)
MVM, Micronucleus test, C57BL/6J mouse bone marrow *in vivo*	+		1850 ip × 2	Richardson *et al.* (1983)
MVM, Micronucleus test, C57BL/6J mouse bone marrow *in vivo*	+		1315 ip × 2	Styles *et al.* (1983)
MVM, Micronucleus test, C3H/C57 mouse bone marrow *in vivo*	+		1315 ip × 2	Styles *et al.* (1983)
MVM, Micronucleus test, BALB/c/CBA mouse bone marrow *in vivo*	+		1315 ip × 2	Styles *et al.* (1983)
MVR, Micronucleus test, Alderley Park rat bone-marrow cells *in vivo*	+		1850 ip × 1	Albanese (1987)
CBA, Chromosomal aberrations, mouse bone-marrow cells *in vivo*	–		15 ip × 1	Manna & Das (1973)
CBA, Chromosomal aberrations, Alderley Park rat bone-marrow cells *in vivo*	+		1850 ip × 1	Albanese (1987)
DLM, Dominant lethal test, A/L and C57BL/6J mice	+		50 ip × 2	Srám *et al.* (1970)
DLM, Dominant lethal test, ICR/Ha Swiss mice	–		2000 ip × 1	Epstein *et al.* (1972)
SPM, Sperm morphology, $B6C3F_1$/CRL mice *in vivo*	–		2630 ip × 5	Wyrobek *et al.* (1981)
SPM, Sperm morphology (CBA×BALB/c)F_1 mice *in vivo*	?		1030 ip × 5	Topham (1981)

[a] +, positive; (+), weak positive; –, negative; NT, not tested; ?, inconclusive

[b] LED, lowest effective dose; HID, highest ineffective dose; in-vitro tests, μg/mL; in-vivo tests, mg/kg bw/day; NG, not given; ip, intraperitoneal

[c] Activation system using human hepatoma (Hep62) S-9; rat liver S-9 was negative

[d] The fluorescent in situ hybridization assay shows ~80% of the micronuclei are centromere-positive compared to ~50% in controls.

exogenous metabolic activation system. In a recent study, it was claimed to be mutagenic to several strains of *S. typhimurium*, in the presence of an exogenous metabolic activation system, when tested in a liquid suspension assay.

In *Drosophila melanogaster*, hexamethylphosphoramide gave positive results in tests for sex-linked recessive lethal mutations, heritable translocations, somatic mutation and differential survival in DNA repair-proficient and -deficient strains. In yeast, it induced mitotic gene conversion. Hexamethylphosphoramide induced micronuclei in newts treated *in vivo*.

In mammalian cells, it induced sister chromatid exchanges, micronuclei and gene mutations *in vitro*. In one study, it induced DNA–protein cross-links in rat nasal epithelial cells treated *in vitro*. In human cells *in vitro*, hexamethylphosphoramide induced micronuclei and sister chromatid exchanges.

In a single study *in vivo*, hexamethylphosphoramide induced sister chromatid exchanges in mouse bone marrow but not in mouse liver. In single studies *in vivo*, hexamethylphosphoramide did not induce chromosomal aberrations in mouse bone marrow, but did so in rat bone marrow. In several independent studies, it induced micronuclei in bone marrow of mice treated *in vivo*. Of two studies in which hexamethylphosphoramide was tested for induction of dominant lethal mutations in mice, one was positive and one was negative. It gave inconclusive or negative results in tests for abnormal sperm morphology in mice.

4.4.3 *Mechanistic considerations*

Studies of the pattern of mutagenicity of hexamethylphosphoramide in *D. melanogaster* strongly suggest that this compound is a DNA cross-linking agent (Vogel & Natarajan, 1995). The cross-linking activity of hexamethylphosphoramide is supported by the detection of DNA–protein cross-links in rat nasal epithelial cells treated *in vitro* (Kuykendall *et al.*, 1995). High-performance liquid chromatographic analysis of DNA extracted from flies injected with [^{14}C]hexamethylphosphoramide revealed no methylation at O^6 or *N*7 of guanine (Vogel *et al.*, 1985). This finding suggests that the formation of DNA adducts by hexamethylphosphoramide may not be the result of simple methylation reactions.

The metabolism of hexamethylphosphoramide in nasal tissues of rats leads to the production of formaldehyde via cytochrome P450-mediated *N*-demethylation (Ashby & Lefevre, 1982; Dahl & Hadley, 1983). Formaldehyde, like hexamethylphosphoramide, is carcinogenic to rat nasal epithelium when given by inhalation and, like hexamethylphosphoramide, induces DNA–protein cross-links in target tissues (IARC, 1995). It is possible, therefore, that metabolism of hexamethylphosphoramide at the target tissue leads to the local production of formaldehyde, which then forms DNA–protein cross-links (and possibly other DNA modifications) which in turn initiate carcinogenesis. However, formaldehyde appears to be significantly more potent (about 60-fold) in forming DNA–protein cross-links than is hexamethylphosphoramide at equimolar concentrations, although the latter is substantially more carcinogenic (by nearly 100-fold) to the rat nasal

epithelium than is formaldehyde (Bogdanffy *et al.*, 1997). This suggests that DNA–protein cross-links alone may not be critical to the mechanism of the carcinogenicity of hexamethylphosphoramide. Based on their studies of the mitogenic and tissue-damaging effects on the rat nasal epithelium of inhaled hexamethylphosphoramide (single exposures or five daily 1-h exposures at 3 ppm), Harman *et al.* (1997) postulated that its high carcinogenic potency could be explained by its ability to liberate formaldehyde intracellularly and to stimulate mitogenesis in the absence of cytoxicity. This is in contrast to formaldehyde, which appears to be carcinogenic only at doses that cause substantial tissue damage and which does not appear to be mitogenic at lower doses that do not damage the nasal epithelium (IARC, 1995). It is argued, therefore (Bogdanffy *et al.*, 1997; Harman *et al.*, 1997), that the stimulus for formaldehyde-induced cell proliferation is cytotoxicity, whereas for hexamethylphosphoramide it is mitogenesis. The efficiency with which promutagenic lesions induced by formaldehyde are converted to mutations would be low, since the death rate of epithelial cells (cytotoxicity) would counteract the birth rate (cell proliferation). In contrast, metabolites of hexamethylphosphoramide that accumulate in the tissue induce a mitogenic response such that the low levels of promutagenic lesions produced from formaldehyde would be more likely to be converted into mutations.

5. Evaluation

No epidemiological data relevant to the carcinogenicity of hexamethylphosphoramide were available.

There is *sufficient evidence* in experimental animals for the carcinogenicity of hexamethylphosphoramide.

Overall evaluation

Hexamethylphosphoramide is *possibly carcinogenic to humans (Group 2B).*

6. References

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